EXHIBIT E

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 51, No. 5, October 15, 2004, pp 738–745
DOI 10.1002/art.20697

ORIGINAL ARTICLE

Randomized, Double-Blind, Placebo-Controlled Glucosamine Discontinuation Trial in Knee Osteoarthritis

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Objective. **To assess the efficacy of glucosamine sulfate in knee osteoarthritis (OA).**
Methods. **A 4-center, 6-month, randomized, double-blind, placebo-controlled glucosamine discontinuation trial was conducted in 137 current users of glucosamine with knee OA who had experienced at least moderate improvement in knee pain after starting glucosamine. Study medication dosage was equivalent to the dosage of glucosamine taken prior to the study (maximum 1,500 mg/day). Followup continued for 6 months or until disease flare, whichever occurred first. The primary outcome was the proportion of disease flares in the glucosamine and placebo groups using an intent-to-treat analysis. Secondary outcomes included time to disease flare; analgesic medication use; severity of disease flare; and change in pain, stiffness, function and quality of life in the glucosamine and placebo groups.**
Results. **Disease flare was seen in 28 (42%) of 66 placebo patients and 32 (45%) of 71 glucosamine patients (difference –3%; 95% confidence interval [95% CI] –19, 14; $P = 0.76$). In the Cox regression analysis, after adjustment for sex, study site, and OA radiographic severity, time to disease flare was not significantly different in the glucosamine compared with placebo group (hazard ratio of flare = 0.8; 95% CI 0.5, 1.4; $P = 0.45$). At final study visit, acetaminophen was used in 27% and 21% of placebo and glucosamine patients, respectively ($P = 0.40$), nonsteroidal antiinflammatory drugs were used in 29% and 30% ($P = 0.92$), and both were used in 20% and 21% ($P = 0.84$). No differences were found in severity of disease flare or other secondary outcomes between placebo and glucosamine patients.**
Conclusion. **In patients with knee OA with at least moderate subjective improvement with prior glucosamine use, this study provides no evidence of symptomatic benefit from continued use of glucosamine sulfate.**

KEY WORDS. Glucosamine; Knee osteoarthritis; Randomized discontinuation trial.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease worldwide. Symptomatic knee OA occurs in 6% of the population older than 30 years (1) and increases in prevalence with age. Knee OA causes significant disability, including work disability (2–5), and is associated with substantial economic costs (6,7). With the aging of the population, the economic burden of OA is projected to increase considerably by the year 2020 (8). Current treatments are limited to nonpharmacologic interventions, such as weight reduction and exercise, pharmacologic

Supported by grants from the Mary Pack Research Fund, Vancouver, British Columbia, Canada and by the Doris Alma Mary Anderson Fund for Geriatric Research, London, ON, Canada. Dr. Cibere's work supported by a Canadian Institutes of Health Research Clinician Scientist Award and a Michael Smith Foundation for Health Research Postdoctoral Fellowship Award.

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Submitted for publication October 22, 2003; accepted in revised form February 9, 2004.

management of pain, and surgical treatment for severe OA. Therefore, the search for and evaluation of new treatments for OA is an important step toward better management of this disease. Glucosamine has been widely publicized in North America and is currently one of the top-selling nutritional supplements. However, the evidence for efficacy of glucosamine is controversial.

Glucosamine has been evaluated for the symptomatic treatment of knee OA in a number of studies (9–20), most of which have reported benefit (9–17). However, systematic reviews of these studies have commented on methodologic issues relating to study design, publication bias, and the tendency for pharmaceutical sponsorship to be associated with positive study findings (21,22). Two trials have reported the benefit of glucosamine on the radiographic progression of OA as well as symptomatic improvement over 3 years (23,24). In contrast, 3 recent studies have reported no efficacy of glucosamine in the treatment of symptomatic knee OA (18–20). The differences in these studies has been highlighted in a recent review of the glucosamine literature by McAlindon in an attempt to provide insight into why clinical trials of glucosamine are no longer uniformly positive (25). However, the conclusion from this review was that more research was needed. As a result, despite numerous studies, the evidence for the efficacy of glucosamine in knee OA is inconclusive.

This study was initiated to assess the efficacy of glucosamine. Because glucosamine is freely available as an over-the-counter nutritional supplement, its use has become widespread in the community. As a result, this study was designed as a randomized discontinuation trial (RDT) (26) to evaluate the effect of continuing or withdrawing glucosamine in patients with knee OA.

PATIENTS AND METHODS

Patients. Participants were recruited through newspaper advertising and local posters. Subjects were included if they met the following eligibility criteria: 1) OA of the knee(s) according to the American College of Rheumatology diagnostic criteria (27), 2) Kellgren-Lawrence grade $\geq$2 on anteroposterior radiograph of the knee (28), 3) current daily use of glucosamine for at least 1 month, 4) at least moderate improvement in knee pain since starting on glucosamine, measured on a 6-point scale of knee pain (worse, unchanged, mildly improved, moderately improved, markedly improved, completely subsided). Subjects were excluded if they met any of the following criteria: 1) chondroitin sulfate use within the previous 2 months, 2) knee injection with hyaluronate in the previous 6 months or with corticosteroids in the previous 3 months, 3) surgical procedure on either knee in the previous 3 months, 4) narcotic analgesic use, 5) uncontrolled medical condition or planned surgery that could interfere with followup, 6) baseline potassium $>$5.3 mEq/liter or baseline creatinine $>$120 mmol/liter.

Study design. The study was a 6-month, randomized, double-blind, placebo-controlled parallel-group glucosamine discontinuation trial performed at 4 centers in Canada. The study was conducted in accordance with the Declaration of Helsinki (1975) and was approved by the Institutional Review Board at each study site. All patients provided written informed consent.

Randomization. A central computer-generated randomization code was produced by a researcher not affiliated with the study. Block randomization with a randomly variable block size of 2–6 was used. The randomization code was forwarded to the manufacturer of the study medication and was used to label the study medication bottles consecutively from 1 to 160. The randomization codes remained sealed until after the blinded analysis had been carried out. Thus, allocation concealment was maintained and study investigators and patients were blinded throughout the study. Eligible subjects were assigned the next consecutive study number.

Intervention. Glucosamine and placebo tablets were supplied by VitaHealth (Winnipeg, Manitoba, Canada). The active drug consisted of glucosamine sulfate formulated as a potassium salt preparation (500-mg tablets). The placebo tablets were indistinguishable from the glucosamine tablets and contained excipients only. Patients were randomized to receive either glucosamine sulfate or placebo. The study medication dosage was equivalent to the dosage of glucosamine taken prior to the study with a maximum of 1,500 mg per day. Patients who used a dosage $>$1,500 mg per day prior to the study were treated with 1,500 mg per day during the study. Compliance with study treatment was evaluated by pill count at each visit, except at week 2. Rescue analgesic medications including acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) were allowed and recorded by the patient in a daily diary. Other concomitant treatments, including chondroitin sulfate and intraarticular injections with corticosteroids or hyaluronic acid, were not allowed during the study. Followup continued for 6 months or until disease flare, whichever occurred first.

Outcome assessments. Following the screening visit and determination of eligibility, patients were assessed at weeks 0 (baseline), 2, 4, 8, 12, and 24 or at any time if a flare occurred. Each study visit included an evaluation of knee symptoms, review of medications and adverse events, an assessment of acetaminophen and NSAID use over the preceding study interval, and a knee examination including warmth, joint effusion, crepitus, joint line tenderness, end-of-range stress pain, and range of motion measured by goniometer. At each visit, patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version VA3.0), which is a validated disease-specific questionnaire frequently used in OA trials assessing pain, stiffness, and function (29); patients also completed the European Quality of Life questionnaire (EQ-5D), a validated generic health assessment tool that includes a utility score and a 0–100 visual analog scale (VAS) (30). Following all assessments, a physician global assessment was recorded, rating patient status on a scale from 1 to 5 as very poor, poor, fair, good, or excellent (31). A determination of whether disease flare had occurred was made at each visit. If a disease flare was present, the patient was withdrawn from the study. At the final study visit, patient blinding was assessed by asking

the patient's opinion whether glucosamine or placebo was received in the study. When all patients had completed the study, a random selection of 11% of glucosamine study drugs (n = 8) and a random selection of 2 placebo study drugs were analyzed for glucosamine sulfate content. The glucosamine sulfate content analysis was performed by JR Laboratories Inc. (Vancouver, British Columbia, Canada) using an internally validated Hamilton high performance liquid chromatography system.

Study outcomes. The primary endpoint was the proportion of patients with disease flare in the glucosamine and placebo groups. Disease flare was defined a priori as either the patient's perception of worsening of symptoms with a concomitant increase by at least 20 mm in WOMAC pain on walking, or a significant worsening in the physician global assessment by at least 1 grade (1–5 scale). This definition of disease flare was determined by study rheumatologists to be a clinically important change in WOMAC. Secondary outcomes included the time to disease flare; change from baseline to flare visit in WOMAC pain, stiffness, function, and total scores; change from baseline to flare in EQ-5D utility and VAS; and the proportion of patients using acetaminophen, NSAIDs, or both in the 2 treatment groups at final study visit. In addition, severity of disease flare was assessed in the placebo and glucosamine groups by comparing mean change scores in WOMAC pain, stiffness, function, total WOMAC, and EQ-5D utility and VAS scores in patients who experienced a flare.

Statistical analysis. Baseline characteristics were compared between the placebo and glucosamine treatment groups. The proportion of patients with disease flare was assessed using the chi-square test. Time to disease flare was evaluated by survival analysis. Kaplan-Meier curves were generated for the placebo and glucosamine treatment groups and the log-rank test was used to test for a statistical difference between the curves. Because of baseline imbalances between treatment groups, a Cox regression analysis was performed with adjustment for imbalanced covariates. The effect of treatment group on the hazard of developing a disease flare was evaluated in an initial univariate model. Sex, study site, and OA radiographic severity were then added to the model to evaluate the effect of treatment on the hazard of developing a disease flare after adjustment for these covariates. In addition, other clinically important covariates were assessed in the Cox regression analysis including age, duration of glucosamine use, glucosamine dosage, duration of OA, and analgesic medication use. The assumptions underlying the proportional hazards model were assessed using residual plots and log-log plots. There was no evidence of violation of any model assumptions.

An intent-to-treat approach was used. It was decided a priori that patients who were lost to followup would be considered to have flared for the purpose of the primary analysis. For the survival analysis, patients lost to followup were right censored, and hence they were followed only to their last visit.

The sample size calculation was based on assumptions of a 10% flare rate in the glucosamine group and a 30% flare rate in the placebo group. With a power of 80% and an alpha error of 5%, a sample size of 62 patients per group was calculated. Under the assumption of a 10% dropout rate, the target for recruitment was 138 patients.

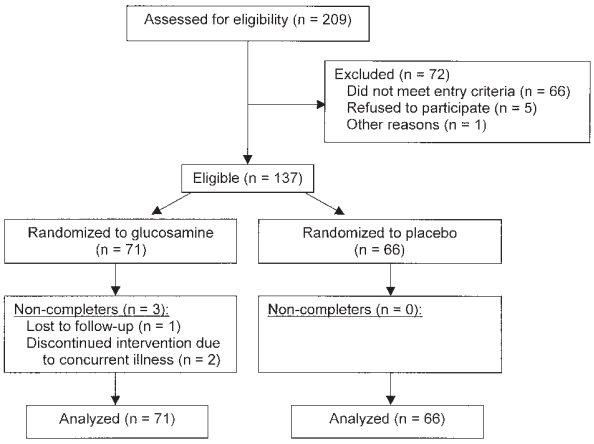

Figure 1. Flow diagram of study enrollment and conduct.

RESULTS

A total of 209 patients were screened for the study (Figure 1). Of these, 137 met the inclusion and exclusion criteria and were randomized to receive glucosamine (n = 71) or placebo (n = 66). In total, 134 patients completed the study to the predefined outcome of disease flare or 6 months of completed followup. Of the remaining 3 patients, 1 was lost to followup after week 4, 1 withdrew from the study at week 2 due to a cerebrovascular accident, and 1 withdrew at week 4 due to a diagnosis of metastatic adenocarcinoma of unknown origin. These 3 patients had been assigned to the glucosamine treatment group and were considered to have flared for the primary analysis.

The baseline characteristics of placebo and glucosamine patients were comparable except for sex and OA radiographic severity (Table 1). Women made up 70% of patients in the placebo group, compared with 44% in the glucosamine group. Mild radiographic knee OA (Kellgren-Lawrence grade 2) was present in 64% of the placebo group and 46% of the glucosamine group. In contrast, moderate OA (grade 3) was present in 33% and 44%, respectively, and severe OA (grade 4) was seen in 3% and 10%, respectively. As a result, patients in the glucosamine group had more severe knee OA based on radiography. However, severity based on WOMAC pain (possible score of 0–500) and function (possible score of 0–1,700) was comparable in the 2 groups with median (range) WOMAC pain scores of 86 (2–279) and 86 (4–301), and median (range) WOMAC function scores of 268 (0–1,376) and 294 (2–1,240) in the placebo and glucosamine groups, respectively (Table 1). Because no analgesic washout was used in this discontinuation trial, these scores, although lower than those reported in standard trials, are consistent with a moderately severely affected patient population, as indicated by the range of scores. The majority of patients in both groups used a glucosamine dosage of 1,500 mg per

Table 1. Baseline characteristics of placebo and glucosamine groups*

	Placebo n = 66	Glucosamine n = 71
Age, mean (range) years	65 (43–88)	64 (40–83)
Female, %	70	44
Body mass index, mean (range) kg/m^2	27 (21–45)	28 (19–49)
Duration of glucosamine use, median (range) years	1.5 (0.1–6.8)	1.7 (0.1–5.4)
Prestudy type of glucosamine, %		
Glucosamine sulfate	94	96
Glucosamine hydrochloride	6	4
Prestudy glucosamine dosage, %		
>1,500 mg per day	5	7
1,500 mg per day	53	61
1,000 mg per day	33	26
500 mg per day	9	6
Duration of physician-diagnosed OA, median (range) years	3 (0–29)	3 (0–29)
Radiographic OA severity, %		
K-L grade 2	64	46
K-L grade 3	33	44
K-L grade 4	3	10
WOMAC pain on walking, median (range) 0–100 mm	12 (0–78)	13 (0–63)
WOMAC pain, median (range) 0–500 mm	86 (2–279)	86 (4–301)
WOMAC function, median (range) 0–1,700 mm	268 (0–1,376)	294 (2–1,240)
WOMAC total, median (range) 0–2,400 mm	414 (26–1,796)	444 (10–1,671)
Analgesic medication use, %		
Acetaminophen only	24	17
NSAIDs only	35	35
Both acetaminophen and NSAIDs	14	16

* OA = osteoarthritis; K-L = Kellgren-Lawrence; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NSAIDs = nonsteroidal antiinflammatory drugs.

day prior to the study, with only 3 (5%) placebo and 5 (7%) glucosamine patients using a larger dosage. The maximum prestudy dosage was 2,000 mg per day. Similarly, the majority of patients had used glucosamine sulfate prior to the study with only 4 (6%) placebo and 3 (4%) glucosamine patients having used prestudy glucosamine hydrochloride.

The primary endpoint of a disease flare in the intent-to-treat analysis was seen in 28 (42%) of 66 patients in the placebo group and 32 (45%) of 71 patients in the glucosamine group (Figure 2). The between-group difference of –3% was not statistically significant (95% confidence interval [95% CI] –19, 14; $P = 0.76$).

No differences were seen for acetaminophen and NSAID use between the placebo and glucosamine groups (Figure 3). At final study visit, acetaminophen was used by 27% and 21% of placebo and glucosamine patients, respectively (difference 6%; 95% CI –8, 20; $P = 0.40$), NSAIDs were used by 29% and 30%, respectively (difference –1%; 95% CI –16, 14; $P = 0.92$), and both acetaminophen and NSAIDs were used by 20% and 21%, respectively (difference –1; 95% CI –15, 12; $P = 0.84$). Dosages of acetaminophen and NSAIDs were also not different between the 2 treatment groups at final study visit (data not shown). Other secondary outcomes of WOMAC pain on walking, pain score, stiffness score, function score, total WOMAC, and quality of life (EQ-5D utility and VAS) were not significantly different in the placebo and glucosamine groups (Table 2).

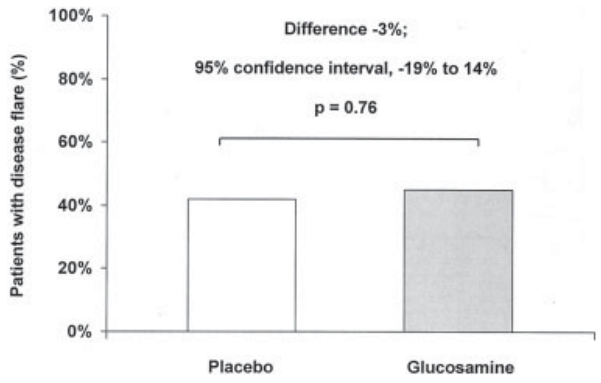

Figure 2. Proportion of disease flare in the placebo and glucosamine treatment groups in the intent-to-treat population.

Time to disease flare, assessed by survival analysis, was also similar in the placebo and glucosamine groups. There were no statistically significant differences in Kaplan-Meier survival curves for patients who continued on glucosamine compared with those who were withdrawn from glucosamine (log-rank test, $P = 0.96$; Figure 4). A univariate Cox regression analysis with treatment group as the explanatory variable revealed a hazard of disease flare of 0.98 (95% CI 0.6, 1.6; $P = 0.93$) in the glucosamine group compared with placebo (Table 3). After adjustment for sex, study site, and OA radiographic severity, there was no difference in the risk of disease flare between the placebo and glucosamine patients (hazard ratio 0.8; 95% CI 0.5, 1.4; $P = 0.45$; Table 3). Age, duration of glucosamine use,

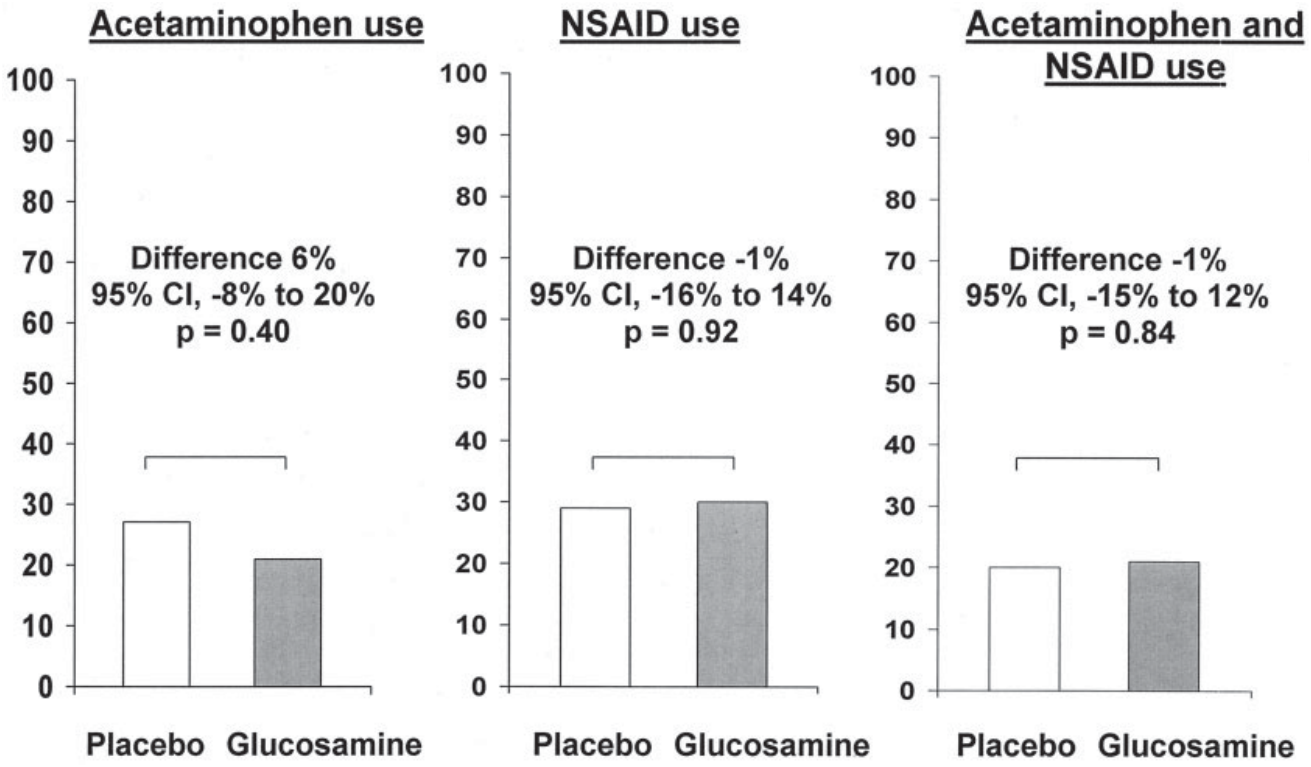

Figure 3. Proportion of analgesic drug use at final study visit in the intent-to-treat population. NSAID = nonsteroidal antiinflammatory drug; 95% CI = 95% confidence interval.

glucosamine dosage, duration of OA, and analgesic medication use were not significant in the Cox regression analysis (data not shown) and hence were not included in the final model.

Severity of disease flare was similar in the placebo- and glucosamine-treated patients who flared (Table 4). There were no statistically significant differences in mean change in WOMAC pain on walking, pain, stiffness, or function scales; total WOMAC score; or quality of life between flare patients in the placebo and glucosamine groups. However, mean change scores of flare patients were substantially different from those of nonflare patients. Worsening of WOMAC and EQ-5D scores was seen in patients who had a flare, as indicated by negative change scores, whereas improvement of these outcomes occurred in patients who did not have a flare, as indicated by positive change scores (Table 4).

Compliance with study drug was excellent. Greater than 80% compliance was seen in 97% of patients receiving placebo and 97% of patients receiving glucosamine. There was no evidence of unblinding at the end of the study. No serious adverse events were reported during the study and

Table 2. Mean change in WOMAC and EQ-5D at final visit compared with baseline and between-group differences in the intent-to-treat population*

	Mean (SD) Change from baseline* mean ± SD			
	Placebo (n = 66)	Glucosamine (n = 71)	Between-group difference (95% CI)	*P*
WOMAC				
Pain on walking, 0–100 mm	−8 ± 25	−5 ± 21	−3 (−11, 4)	0.40
Pain scale, 0–500 mm	−28 ± 104	−25 ± 98	−3 (−37, 32)	0.88
Stiffness scale, 0–200 mm	6 ± 48	2 ± 42	4 (−11, 20)	0.57
Function scale, 0–1,700 mm	−63 ± 318	−58 ± 270	−5 (−105, 94)	0.92
Total scale, 0–2,400 mm	−85 ± 453	−81 ± 388	−4 (−145, 139)	0.96
EQ-5D				
Utility score, 0–1	−0.04 ± 0.20	−0.03 ± 0.16	−0.01 (−0.07, 0.05)	0.68
Visual analog scale, 0–100	−2 ± 12	0.1 ± 16	−2 (−7, 3)	0.42

* Positive mean change indicates improvement, negative mean change indicates worsening. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D = European Quality of Life questionnaire; 95% CI = 95% confidence interval.

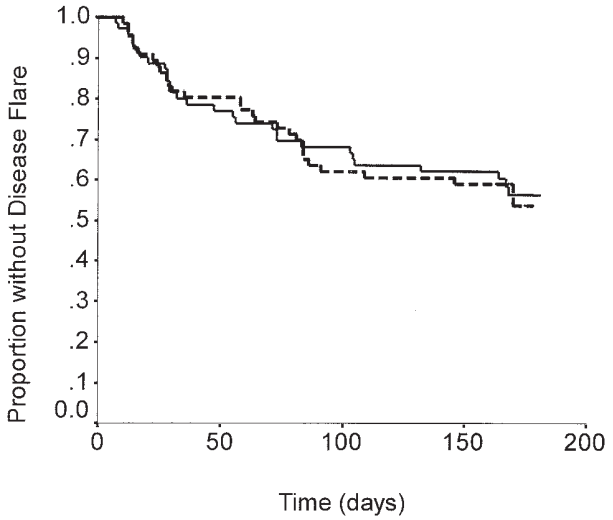

Figure 4. Kaplan-Meier survival curves for time to disease flare in the placebo (**dashed line**) and glucosamine (**solid line**) groups. Log-rank test, $P = 0.96$.

there were no differences in adverse events between the glucosamine and placebo groups. Because of the discontinuation design of this study, minimal adverse effects were expected, since all subjects had previously tolerated glucosamine. Mean glucosamine sulfate content was found to be 618 mg per tablet in the glucosamine samples and 0 mg per tablet in the placebo samples.

DISCUSSION

Efficacy of glucosamine in knee OA has been reported predominantly in trials with pharmaceutical sponsorship (21). With recent publications of glucosamine studies reporting no therapeutic value (18–20), the issue of whether glucosamine is efficacious has become more controversial. In this study, we found that knee OA disease flare occurred as frequently, as quickly, and as severely in patients who were randomized to continue receiving glucosamine compared with those who received placebo. As a result, the efficacy of glucosamine as a symptom-modifying drug in knee OA is not supported by our study.

The randomized discontinuation trial approach has been used infrequently to demonstrate efficacy. A key underlying assumption for the RDT study design is that the disease process will worsen or flare when the drug is discontinued. This presumes that the disease under study has not been cured by the drug treatment prior to the trial. Although glucosamine is frequently promoted as a disease-modifying drug, there is no evidence that it is curative, and hence an RDT study design is appropriate. A 6-month study design was felt to be sufficient to allow for disease flares to occur. Because pain relief occurs within 2–3 months of treatment with glucosamine, it seems reasonable to expect development of a flare within a similar timeframe after discontinuation of glucosamine, assuming no curative effect. Because patients in this study were enrolled only if they had subjective improvement while taking glucosamine, the question of whether glucosamine has an initial beneficial effect cannot be answered. Any initial perceived benefit may have been due to a placebo response or natural fluctuation in symptoms over time and hence a null finding would be expected in a discontinuation trial. Alternatively, a temporary initial benefit could be due to glucosamine itself or another component of the nutritional supplement, such as sulfate. However, even if an initial benefit had been derived from glucosamine or sulfate, our findings suggest that there is no evidence of benefit with continued use of glucosamine sulfate for the symptomatic treatment of knee OA.

Table 3. Multivariate hazard ratio of disease flare in the Cox regression analysis*

Variables	Hazard ratio (95% CI)	*P*
Univariate analysis		
Placebo	1.0	
Glucosamine	0.98 (0.6, 1.6)	0.93
Multivariate analysis		
Placebo	1.0	
Glucosamine	0.8 (0.5, 1.4)	0.45

* The multivariate analysis was adjusted for sex, study site, and radiographic severity of osteoarthritis. 95% CI = 95% confidence interval.

Our negative study findings need to be interpreted in the context of the observed confidence interval, which indicates with 95% confidence that a true difference in proportion of flares is no greater than 14% in favor of glucosamine. Because this study was designed to detect a clinically important difference of 20%, these findings are consistent with our a priori null hypothesis.

Furthermore, our negative study findings cannot be explained by a lack of compliance, in view of the fact that 97% of study participants had excellent compliance. Contamination with nonstudy glucosamine is also an unlikely explanation, because the study procedures were clearly understood by participants, the use of all medications was ascertained at each study visit, and participants understood the importance of rigorously evaluating the efficacy of glucosamine. Similarly, cointerventions were not allowed in the study and no protocol violations occurred. Hence, this is an unlikely explanation for our negative findings.

A potential bias toward nonefficacy occurred because patients lost to followup were considered to have flared according to our a priori decision. Because all 3 patients lost to followup were in the glucosamine group, this resulted in more flares in the glucosamine group and hence introduced a bias toward nonefficacy of glucosamine. However, even with the exclusion of these 3 patients, there was no difference in the proportion of flares in the glucosamine and placebo groups.

In addition, if glucosamine hydrochloride has no or minimal efficacy compared with glucosamine sulfate, the use of glucosamine hydrochloride prior to the study may result in a study finding of no difference. Only 4 placebo and 3 glucosamine patients had used the hydrochloride formulation of glucosamine prior to the study and similar proportions experienced a flare (2 patients in each group). Exclusion of these 7 patients did not change the results.

Table 4. Mean change scores in patients who did not experience a flare and those who did in the intent-to-treat population and comparison of severity of change in placebo and glucosamine patients who experienced a flare*

	Change from baseline mean ± SD				Between group difference (95% CI) for placebo and glucosamine flarers	*P*
	No flare		Flare			
	Placebo (n = 38)	Glucosamine (n = 39)	Placebo (n = 28)	Glucosamine (n = 32)		
WOMAC						
Pain on walking, 0–100	5 ± 15	5 ± 12	−25 ± 26	−17 ± 23	−8 (−21, 4)	0.20
Pain subscale, 0–500	24 ± 75	30 ± 47	−97 ± 98	−92 ± 103	−5 (−58, 47)	0.83
Stiffness subscale, 0–200	20 ± 42	25 ± 34	−13 ± 50	−26 ± 34	13 (−9, 36)	0.24
Function subscale, 0–1,700	69 ± 264	96 ± 178	−243 ± 300	−246 ± 243	3 (−138, 143)	0.97
Total scale, 0–2,400	114 ± 368	151 ± 237	−354 ± 422	−364 ± 347	10 (−188, 209)	0.92
EQ-5D						
Utility score, 0–1	0.02 ± 0.18	0.02 ± 0.14	−0.13 ± 0.2	−0.10 ± 0.16	−0.03 (−0.13, 0.06)	0.46
Visual analog scale, 0–100	2 ± 9	6 ± 14	−6.6 ± 15	−6.9 ± 16	0.3 (−8, 8)	0.95

* Positive mean change indicates improvement, negative mean change indicates worsening. 95% CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D = European Quality of Life questionnaire.

Finally, because OA disease activity can fluctuate naturally, a difference between treatment groups may not be appreciable based solely on the primary outcome of disease flare. For this purpose, we evaluated as secondary outcomes the severity of change in WOMAC pain, stiffness, and function scores, as well as the time to disease flare in the placebo and glucosamine groups. However, no differences were found in the severity of disease flare or time to disease flare, lending further support to our conclusion of no symptomatic benefit from continued glucosamine use in knee OA.

Our findings are in keeping with other recent studies with negative results (18–20). Houpt et al (18) evaluated a population of knee OA patients with predominantly early radiographic changes in which 74% of patients had Kellgren-Lawrence grade 1 or 2 changes (28). They reported no significant difference in WOMAC pain, stiffness, or function scores after 2 months of treatment with glucosamine compared with placebo. In the study by Rindone et al (19), in which approximately half of the patients had early knee OA (Kellgren-Lawrence grade 1 or 2), they found no differences in pain at rest and pain on walking after 2 months of treatment with glucosamine or placebo. The most recent study by Hughes and Carr (20) evaluated patients with more advanced knee OA—60% of the study population had moderate to severe knee OA (Kellgren-Lawrence grade 3 or 4). In that study, no differences were seen between glucosamine and placebo groups in pain, use of analgesic medications, or the proportion of responders to treatment over a 6-month study period. These findings suggest that the radiographic stage of OA is likely not a factor in nonresponse to glucosamine treatment. This is further supported by the results of our Cox regression analysis, in which adjustment for radiographic OA severity did not have a significant effect on the result of treatment as a predictor of disease flare and hence glucosamine was found to be nonefficacious regardless of radiographic OA severity. Similarly, glucosamine dosage, duration of glucosamine use, and analgesic medication use were not significant in the Cox regression analysis and hence did not have an effect on the risk of disease flare in our study.

There are a number of strengths and limitations of this study. As discussed previously, a disadvantage of the RDT study design is that any initial benefit of glucosamine cannot be evaluated. A further limitation is that the RDT study design has never been used in OA. As a result, no validated definition of disease flare exists. Our definition of disease flare was adopted a priori and was thought to be of clinical importance. Moreover, since the initiation of our study, additional publications have lent support to our choice of flare criteria (31,32). The minimal clinically perceptible difference (MCPD) in WOMAC pain on walking was reported by Ehrich et al (31) to be 11 mm on a 100-mm VAS. Similarly, the MCPD for physician global assessment was reported to be 0.43 on a 0–4 Likert scale (31). As a result, the definition for disease flare used in this study was adequate to detect a difference in patient status. Furthermore, in the recent Osteoarthritis Research Society International (OARSI) guidelines on response criteria, the committee recommended that treatment response in an NSAID trial be defined as an absolute decrease in VAS pain by 20 mm in association with a relative decrease of pain by 45% (32). An absolute difference of 20 mm should therefore be applicable as a flare criterion and hence the OARSI guidelines lend further support to the validity of our choice of flare criteria.

The need for rescue medication in a discontinuation trial may be seen as a further limitation due to the potential confounding effect. However, analgesic medication use was included in the secondary analysis of the data and was similar in the placebo and glucosamine groups. In addition, the inclusion of acetaminophen and NSAID use in the Cox regression analysis showed that there was no confounding effect. Furthermore, the use of acetaminophen and NSAIDs may be viewed as a strength of this study, because their use reflects common practice in OA. If a benefit of glucosamine cannot be detected under real world circumstances, then the applicability of glucosamine is limited, even if it is found to be efficacious.

There are several advantages to using an RDT study design, including the ability to test the efficacy of a drug that is widely used and minimization of exposure to pla-

cebo (26). Furthermore, a particular strength of this study is the selection of patients with at least moderate perceived response to prior glucosamine treatment. The use of such a selective population allows for a more efficient trial, since patients who have previously responded to treatment with glucosamine are more likely to flare on discontinuation of glucosamine than nonresponders. Therefore, a treatment difference between glucosamine and placebo, if one exists, can be shown more easily in such a preselected population (26). Despite this greater ability to show efficacy, our study results were negative and hence this serves to strengthen our conclusions.

In summary, for patients with knee OA with at least moderate subjective improvement with prior glucosamine use, this study provides no evidence of symptomatic benefit from continued use of glucosamine sulfate over and above that found with placebo.

ACKNOWLEDGMENTS

We would like to thank all the study participants for their interest and participation and we would like to acknowledge the late Leonard Marks for his assistance in obtaining the medication. We thank Allen Lehman for providing the randomization codes and JR Laboratories Inc. for performing the glucosamine sulfate content analysis.

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